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EXAMINER	
ISSAC, ROY P	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 09/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/781,705	MAREK ET AL.	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *1,2,25 and 27-29* is/are allowed.

6)☒ Claim(s) *3-24 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/20/04 &5/26/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a continuation of 09/850,081 filed 05/08/2001, issued as U.S. Patent No. 6,762,202, which claims benefit of the provisional application, 60/202,935 filed 05/09/2000.

Claims 1-29 are currently pending and are examined on the merits herein.

Claim Objections

Claims 3-16 are objected to because of the following informalities: Claim 3 depends from itself and claims 4-16 depend from claim 3. Appropriate correction is required. Claim is examined as depending from its only preceding composition claim, claim 2.

Claim 16 is objected to because of the following informalities: The term "denaoyl" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-24 and 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had full possession of the claimed invention.

The claims herein are drawn to compositions containing the claimed compounds in claim 1, and penetration enhancers, at least one compound that donate, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide and substrates of nitric oxide synthase and vasoactive agents.

The specification as originally filed does not provide adequate support for the generic claims herein. The specification merely describes the synthesis of the composition of claim 2. The specification does not provide adequate support for the combination of specific compounds of claim with compounds described by generic and functional language in claims 3-16, 22-24 and 26.

The claims merely uses language that describe a significant portion of the known and unknown organic compounds that may be useful in the pharmaceutical industry to be used in combination with the composition of claim 2. There are no examples of any particular combination of the composition of claim 2 with any other particular compound claimed in claims 3-16, 22-24 and 26. The Federal Circuit held in *In Re Curtis* that "a patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when... the evidence indicates ordinary artisans would

not predict the operability ....of any other species." (See *In Re Curtis* 354 F.3d 1347, 69, USPQ2d 1274, 2004). In the instant case the written description support is only available for the synthesis of the compounds in claim 1 and its combination with a pharmaceutically acceptable carried claimed in claim 2. Based on the specification as originally filed, one of ordinary skilled in the art will not recognize that the applicants were in possession of the combination of compounds claimed in claims 3-16. The claimed combination of compositions of claim 2 with other compounds described by generic and functional languages in claims 3-16, 22-24 and 26 are deemed as not to adequately described. Thus, one of ordinary skill in the art would not predict the operability of the combination of claimed compounds. Thus, the claimed composition is seen to clearly lack written description support.

Furthermore, the applicants do not provide written description support for the use of the compounds of claims 1-2 for the treatment of any disease or disorder. The claimed compounds and their compositions containing pharmaceutical acceptable carriers are not shown to have any biological affect *in vitro* or *in vivo* on any proteins or DNA or mammals or humans or microorganisms. The only example of any biological study involves S-nitrosoglutathione. (Specification, Examples 7-9, Page 40). One or ordinary skill in the art will not consider compounds of claims 1-2 to have strong structural similarity with s-nitrosoglutathione. As such, one of ordinary skill in the art will not expect similar biological property for the compounds of claims 1-2. One of ordinary skill in the art will not view the applicants to have had possession of the

invention from the specification as originally filed. The claimed methods of use of the compounds clearly lack written description support.

Claims 3-24 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition containing a compound of claim 1 and further comprising a pharmaceutically acceptable carrier, does not reasonably provide enablement for all compounds and compositions that can be considered as a "penetration enhancer" or a "compound that donates transfers or releases nitric oxide" or "elevates exogenous levels of endothelium-derived relaxing factor" or "stimulates endogenous synthesis of nitric oxide" or "is a substrate for nitric oxide synthase" or any "vasoactive agent." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to the compositions that contain one of the compounds of claim 1 and other ingredients including penetration enhancers, compounds that transfers or releases or donates nitric oxide or elevates endogenous levels of endothelium-derived relaxing factor or compounds that stimulates endogenous synthesis of nitric oxide or is substrates for nitric oxide synthase and vasoactive agents. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The instant application relates to compounds and compositions used for the treatment of sexual dysfunction.

The state of the prior art:

The effect of glutathione and nitrosoglutathione on sexual dysfunction is well known. (Demopolous et. al. U. S. Patent No. 6,204,248; PTO-892). When glutathione or nitroso-glutathione is placed in the male urethra, the glutathione or glutathione derivative is absorbed. The vasodilatory effects of nitroso-glutathione, which is formed by interaction of glutathione with nitric oxide or provided directly, vasodilates the penis, resulting in an erection. Thus, a urethral glutathione or nitroso-glutathione suppository has potential for the treatment of impotence. Glutathione or nitroso-glutathione may also be used to treat female sexual dysfunction. Direct application of glutathione or nitroso-glutathione to the mucous membranes, for example, as a cream or in a gel formulation, will result in local

vasodilation, lubrication, and engorgement of erectile tissue. (Demopolous et. al., Column 73, lines 55-68). Furthermore, the effects of various pharmacological agents which act to increase the production of nitric oxide, for example the substrate for formation of nitric oxide, the amino acid arginine, the stability of nitric oxide in the blood, or the effect of nitric oxide, may be used synergistically. Likewise, drugs which act on differing systems, such as the central nervous system and peripheral vascular system, may also be used synergistically. Thus, glutathione may be used alone or in combination to achieve its effects on the circulatory system and vascular tissues. (Demopolous et. al., Column 74, lines 1-10).

The relative skill of those in the art:

The relative skill of those in the art is high, with a typical practitioner having obtained a PhD, M.D. or equivalent advanced degree.

The predictability or lack thereof in the art:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that the recitation encompasses

thousands of compositions with varying effects and unknown side effects. As such, each composition will need to be individually evaluated for activity.

The breadth of the claims:

The claims 3-24 and 26 are very broad because, the claims merely uses functional and generic language that describe a significant portion of the known and unknown organic compounds that may be useful in the pharmaceutical industry to be used in combination with the composition of claim 2.

The amount of direction or guidance presented:

The specification describes in functional and generic language a myriad of organic compounds. However, no guidance is provided for the use of any particular compound from the generic class or the compounds described by the functional language in combination with the compounds of claim 1, or composition of claim 2. As such, one of ordinary skill in the art will need to perform substantial experimental effort to determine which of the particular compounds among the thousands of compounds encompassed by the generic and functional language in claims 3-16 will be useful in combination with the compounds of claims 1 and 2.

Claims 3, 4, 8, 11-14, 22-24 and 26 describes the compounds to be used in combination with the compounds/compositions of claim 2 in functional language; "at least one penetration enhancer", "at least one compound that

donates, transfers or releases nitric oxide," "elevates endogenous level of endothelium-derived relaxing factor," "stimulates endogenous synthesis of nitric oxide", "substrate for nitric oxide syntheis", "vasoactive agents".

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to

fully predict possible physiological activities of any compounds having claimed functional properties in the pharmaceutical compositions herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human)

Combination therapy, and drug-drug interactions are known in the art to have various effects, and when physicians use several drugs in combination, they face the problem of knowing whether a specific combination in a given patient has the potential to result in an interaction, and if so, how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences on an interaction if they are adverse. A potential drug interaction refers to the possibility that one drug may alter the intensity of the pharmacological effects of another drug if given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs, or the appearance of new effects, which is not seen with either drug alone. The frequency of significant beneficial or adverse effects is unknown. The interaction between the drugs may be pharmacokinetic, i.e. alteration of the absorption, distribution, or elimination of one drug by another, or may be pharmadynamic, i.e. interactions between agonists and antagonists at drug receptors. The most important drug-drug interactions occur with drugs that have serious toxicity and low therapeutic index, such that relatively small changes in drug level can have significant

adverse consequences. Additionally, drug-drug interactions can be clinically important if the disease being controlled with the drug is serious or potentially fatal if left under treated. Drugs are known to interact at any point during their absorption, distribution, metabolism, or excretion; the result being an increase or decrease in concentration of the drug at the site of action. As individuals vary in their rates of disposition of an given drug, the magnitude of an interaction that alters pharmacokinetic parameters is not always predictable, but can be very significant. See Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Medical Publishing Division, 2001, pages 54-56. **Thus, the teachings of the book clearly support that the instant claimed invention, administering a** combination of any "one or more inhibitors of CYP 450" and the compound of formula I to a human **is highly unpredictable.**

The presence or absence of working examples:

The specification describes the synthesis of the compounds claimed in claim 1 and claims 27-29. (Specification, Pages 36-38, Examples 1-2). The specification does not provide any examples of compositions that further comprises any other compounds, as claimed in claims 3-16, and 22-24 and 26.

Furthermore, the applicants do provide any examples of the use of the compounds of claims 1-2 for the treatment of any disease or disorder. The claimed compounds and their compositions containing pharmaceutical acceptable carriers are not shown to have any biological affect *in vitro* or *in vivo*

on any proteins or DNA or mammals or humans or microorganisms. The only example of any biological study involves S-nitrosoglutathione. (Specification, Examples 7-9, Page 40). One or ordinary skill in the art will not consider compounds of claims 1-2 to have strong structural similarity with s-nitrosoglutathione. As such, one of ordinary skill in the art will not expect similar biological property for the compounds of claims 1-2.

The quantity of experimentation necessary:

One of ordinary skill in the art will need to perform substantial experimental effort to determine which of the particular compounds among the thousands of compounds encompassed by the generic and functional language in claims 3-16 will be useful in combination with the compounds of claims 1 and 2. The specification does not provide clear guidance to one or ordinary skill in the art to determine which of the thousands of possible compounds encompassed by the functional and generic language in claims 3-16 will be useful in combination with the two compounds of claim 1 or further in combination with a pharmaceutically acceptable carrier.

Therefore, in view of the *Wands* factors as discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in ***undue experimentation*** to achieve methods of regulating the condition of skin

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-16, 22-24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3, from which claims 4-16 depends, recites "further comprising at least one penetration enhancer, at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, or a pharmaceutically acceptable salt thereof and/or at least one vasoactive agent..." From this recitation one of ordinary skill in the art will not be able to ascertain whether the claim refers to one compound that possess all the recited qualities or a combination of a compound that possess the penetration enhancing quality and another compound that possess the qualities "donates, transfers or releases nitric oxide" and another compound with the qualities "elevates endogenous levels of endothelium-derived relaxing factor" and yet another with the quality, "stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase". As such, said recitations render the claim indefinite.

Claims 3-16, 22-24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites phrases "penetration enhancer", "compound that donates, transfers or

releases nitric oxide", "elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthesis". Said phrases do not convey a structural formula or chemical name to one of ordinary skill in the art. Even though the specification defines these terms in functional terms, it does not provide structural formula or chemical names of the compounds with said properties. As such, one of ordinary skill in the art would not be apprised of the metes and bounds of claimed invention.

Allowable Subject Matter

Claims 1-2, 25 and 27-29 are allowed.

The following is a statement of reasons for the indication of allowable subject matter: The compounds claimed in independent claims 1 and 27-29 are novel and unobvious over the prior art.

Furthermore, the instant specification is deemed to provide the enabling information to practice invention herein without undue experimentation. Examples 2a-e provides methods of synthesis and characterization for the compounds in claims 1 and 27-29. (Specification, Page 27-28). A kit is also described in the specification. (Specification, Page 35 lines 25-30).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

9/21/06

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